FDA Approves First Gene Therapy for Cancer

Kymriah, a novel CAR-T therapy, helps the immune system recognize and fight cancer.

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On August 30 the Food and Drug Administration (FDA) approved a groundbreaking new type of cancer immunotherapy for the treatment of children and young adults with advanced leukemia. Kymriah, also known as tisagenlecleucel or CTL019, is the first chimeric antigen receptor T cell (CAR-T) gene therapy to win FDA approval.

CAR-T therapy involves removing a sample of a patient's white blood cells, genetically reprogramming them to attack cancer cells and putting them back into the body. Novartis set the price for Kymriah at $475,000, raising questions about how patients will be able to access this kind of highly effective but expensive personalized therapy.

"We're entering a new frontier in medical innovation with the ability to reprogram a patient's own cells to attack a deadly cancer," said FDA Commissioner Scott Gottlieb, MD. "New technologies such as gene and cell therapies hold out the potential to transform medicine and create an inflection point in our ability to treat and even cure many intractable illnesses."

Kymriah was approved for the treatment of children and young adults up to age 25 with B-cell precursor acute lymphoblastic leukemia (ALL) that is refractory (not responding to treatment) or has relapsed twice or more. ALL is the most common childhood cancer in the United States, with around 3,100 cases diagnosed annually, and existing treatments are not very effective for patients who relapse or develop advanced disease. Novartis is also evaluating Kymriah for adults with B-cell lymphoma and other blood cancers.

In July, the FDA's Oncologic Drugs Advisory Committee heard testimony from researchers, parents of children with leukemia and Novartis representatives about the effectiveness, safety concerns and manufacturing process for Kymriah. Among them was the father of Emily Whitehead, who was the first patient to be treated with CAR-T therapy at age 6 and who remains in remission more than five years later.

CAR-T uses gene therapy to modify an individual's killer T cells, the main soldiers of the immune

system, making them better able to find and kill cancer cells. T cells are first extracted from the blood using a process known as leukapheresis. These cells are frozen and shipped to a manufacturing facility. Inactivated HIV is used to insert a gene into the T cells that enables them to target the CD19 antigen on leukemia cells. The modified T cells are then multiplied in the laboratory and infused back into the patient.

In the Phase II ELIANA trial, which enrolled children with advanced B-cell ALL who had received multiple prior therapies and in many cases had undergone bone marrow transplants, 83 percent of the 63 treated patients achieved complete remission within three months, and three quarters remained cancer-free after six months.

Safety issues are a concern with any new type of treatment, and CAR-T has come under scrutiny after several adults in clinical trials of other companies' CAR-T therapies died from cerebral edema, or brain swelling.

Unleashing genetically modified T cells not only can kill cancer cells but also can lead to an excessive immune response that harms healthy tissue. This cytokine release syndrome, or "cytokine storm," can cause symptoms ranging from fever and flu-like side effects to neurological problems and organ failure. In addition, Kymriah attacks normal B cells that produce antibodies along with abnormal leukemia B cells, so treated patients are at increased risk for infections.

About half of the children in the ELIANA study experienced cytokine release syndrome, and 18 percent experienced neurological side effects, in many cases severe. But these were generally managed successfully, and there were no reported cases of brain swelling or treatment-related deaths.

To help manage the side effects of Kymriah, the FDA also granted expanded approval of Genentech's immunosuppressive drug Actemra (tocilizumab) to treat severe cytokine release syndrome in patients age 2 years and older. In clinical trials of CAR-T therapy, two thirds of patients experienced complete resolution of cytokine release syndrome within two weeks after receiving Actemra, according to the FDA.

The FDA will require that hospitals administering Kymriah must be specially certified, staff must be trained to recognize and manage cytokine release syndrome and tocilizumab must be available for immediate administration.

CAR-T therapy is labor- and technology-intensive treatment that is customized for each patient. Novartis said it expects that its manufacturing facility in Morris Plains, New Jersey, will be able to produce an adequate supply of Kymriah, which will be available at around 30 centers in the United States by the end of the year.

With its one-time price of $475,000, Kymriah will be among the most expensive cancer treatments on the market, and patient advocates have raised concerns about how it will be covered by public payers and private insurers. However, its cost compares favorably with that of bone marrow

transplants, which can run up to $500,000 or more.

Novartis said it will offer patient assistance programs and is working with the Centers for Medicare and Medicaid Services to develop an outcomes-based approach in which the government will pay for CAR-T treatment only if a patient responds within a month.

Other companies, including Kite—which will soon be purchased by Gilead Sciences—Bluebird Bio and Juno Therapeutics, are also developing CAR-T therapies. Kite has requested FDA approval of its KTE-C19 for adults with non–Hodgkin lymphoma and has also seen good results in a study of KTE-C19 for adults with relapsed or refractory ALL. Juno recently reported promising data for its JCAR017 in adults with non–Hodgkin lymphoma.

Although Kymriah was approved for just a small population of children with leukemia who don't respond to other therapies, it represents a revolutionary new approach to cancer treatment that will likely see broader use in the future, especially if scaling up production can reduce its cost.

To read a Novartis press release about Kymriah approval, click here.

To read an FDA press release about Kymriah approval, click here.

To see the FDA briefing document on Kymriah, click here.
